UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,481	03/05/2001	Frank Hulstaert	11362.0034.P	8708

7590 04/03/2003

Patricia A Kammerer
Howrey Simon Arnold & White
750 Bering Drive
Houston, TX 77057-2198

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 04/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/786,481	Applicant(s) HULSTAERT ET AL.	
	Examiner Christopher Nichols, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,8,9 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 6, 8, 9, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 12 March 2003 (Paper No. 8) has been entered in full. Claims 1, 5, 6, 8, 9, and 11 have been amended and claims 2-4, 7, 10, and 14-17 have been cancelled. Claims 1, 5, 6, 8, 9, and 11 are under examination.

2. The English summary of **Reference #C3** of the Information Disclosure Statement (Paper No. 3, 5 March 2001) has been considered.

3. The Examiner acknowledges that the effective filing date of the instant application is 7 September 1999 (PCT/EP99/06592) and the priority date of the instant application is 8 September 1998 (EUROPE 98870190.0). The erroneous statement as set forth at ¶5 of the previous Office Action (Paper No. 7, 16 December 2002) was due to a typographical error.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

5. The objection to the Declaration as set forth at pp. 4 ¶7 of the previous Office Action (Paper No. 7, 16 December 2002) is *withdrawn* in view of Applicant's replacement Declaration (Paper No. 8, 12 March 2003).

6. The objection to the Drawings as set forth at pp. 4 ¶8 of the previous Office Action (Paper No. 7, 16 December 2002) is *withdrawn* in view of Applicant's submission of replacement drawings (Paper No. 8, 12 March 2003).

7. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 5, 8, and 11 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that the specification and prior art are enabling (pp. 11-22 "**V. Rejection under 35 U.S.C. §112: '2. Correlation: size of infarction and CSF tau levels" 'In part 15', 'Part 22', Part 23', Part 27', and 'Part 31'**).

8. The Applicant's argument has been taken into consideration and is *persuasive*. The Examiner has *withdrawn* the rejection of claims 1, 5, 8 and 11 under 35 USC §112 ¶1 as it pertains to CNS damage caused by CNS tumors, anoxia, and ischemia.

9. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 2, 3, 4, 7, 10, 14, 15, 16, and 17 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that the aforementioned claims have been cancelled and the rejection is therefore moot (pp. 11-22 "**V. Rejection under 35 U.S.C. §112: '2. Correlation: size of infarction and CSF tau levels" 'In part 16', 'In part 17', In part 18' 'Part 21', 'Part 25', 'Part 26', and 'Part 30'**).

10. The Applicant's argument has been taken into consideration and is *persuasive*. The Examiner has *withdrawn* the rejection of claims 2, 3, 4, 7, 10, 14, 15, 16, and 17 under 35 USC §112 ¶1 due to cancellation of said claims by Applicant (Paper No. 8, 12 March 2003).

11. The rejection of claims 1, 6, 8, 9, and 11 under 35 USC §112 ¶2 as set forth at pp. 18 ¶33 of the previous Office Action (Paper No. 7, 16 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 8, 12 March 2003).

12. The rejection of claims 1, 2, and 3 under 35 USC §102(b) as set forth at pp. 18-19 ¶34 of the previous Office Action (Paper No. 7, 16 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 8, 12 March 2003).

Maintained Objections And/Or Rejections

13. Claims 1, 6, and 9 are rejected under 35 U.S.C. §112 ¶1 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 7, 16 December 2002). Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

14. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that: (a) invention pertains to the detection of "total tau" in CSF samples, (b) "a broad survey of the phosphorylated tau levels in normal or unaffiliated patients" is not the subject of the present invention, (c) all examples in the application related to the detection of tau, independent of phosphorylation, (d) the present invention is drawn to the comparison of the CSF level of tau in individuals with brain damage relative to healthy individuals, (e) the present claims are drawn only to the detection of tau in cerebrospinal fluid (CSF) (pp. 5-7 "**V. Rejection under 35 U.S.C. §112: 'A'**").

15. The Examiner *accepts* the argument that the Applicant has provided sufficient guidance for a skilled artisan to measure "total tau", regardless of phosphorylation state or truncation, in

the cerebrospinal fluid of patients and to compare the measured values of "total CSF tau" between patients.

16. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that: (f) the Examiner provided no support to support a reasonable level of doubt that the claimed invention would work, (g) the present invention shows the correlation between CNS damage caused in an individual by a neurological ailment or injury and the CSF level of tau in said individual, (h) the Specification provides sufficient data to support the assertion that the CSF-tau levels are not random and in fact show a correlation between CSF-tau levels and the degree of CNS damage (pp. 7-8 "**V. Rejection under 35 U.S.C. §112: 'In part 13'**").

17. The Applicant's argument has been taken into consideration and is not persuasive for the following reasons. The Examiner *maintains* the rejection of claims 1, 6, and 9 under 35 USC §112 ¶1 not due to any personal knowledge unbeknownst to the Applicant but supported by the instant specification and prior art supplemented by articles from the literature concerning the alleged connection between tau and specific types of CNS damage.

18. As for the correlation between CNS damage and tau levels, neither the prior art nor the Specification present any evidence that tau is correlated to CNS damage resulting from "*invasions or metastasis of the CNS*" and damage due to "*chemical agents*". Furthermore the Examiner maintains that the tau CSF levels do not show any discernable pattern that would allow a skilled artisan to make any sound judgment concerning "*invasions or metastasis of the CNS*" and damage due to "*chemical agents*". In addition, the Applicant has not satisfactorily defined "*invasions or metastasis of the CNS*" and damage due to "*chemical agents*" such that a skilled

artisan would be assured that a particular species would fit into the wide geneses of "*invasions or metastasis of the CNS*" and damage due to "*chemical agents*".

19. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that: '**a)**' patients with clear CNS invasion show clear, non-random elevated CSF-tau levels about the "cutoff value (312 pg/mL)" as illustrated in Table 1, (pp. 8-9 "**V. Rejection under 35 U.S.C. §112: '1. Correlation: CNS Invasion with CSF tau levels**'").

20. The Applicant's argument has been taken into consideration and is not persuasive for the following reasons. The Examiner *maintains* the rejection of claims 1 and 6 under 35 USC §112 ¶1 as it pertains to "*invasions or metastasis of the CNS*". In fact, in Table 4 (pp. 17) of the Specification a patient with "metastasis of breast cancer" had a tau level of 150 pg/mL, a level that is 48% of the "cutoff value (312 pg/mL)" for controls as presented by Applicant. As for the "Controls" presented by the Applicant in Table 4 of the Specification (pp. 18-19) the "total tau" levels ranged from 37-665 pg/mL, the sample having a median score of 167 pg/mL, a standard deviation of 148 pg/mL, and a mean (or arithmetic average) of 206 pg/mL. Thus it is not clear what statistical significance absent evidence from the prior art that can be assigned to the Applicant's assertion that 312 pg/mL is a "cutoff value" for Control patients when 3 patients show higher total tau levels than 312 pg/mL.

21. In response to the date presented in Table 1 (pp. 9), the first two patients are presented with only relative terms, of little or no use to determine a correlation. Next, the patients as presented suffer from a wide range of ailments including medulloblastoma, germinoma, rhabdomyosarcoma, and retinoblastoma with "CNS involvement". It is not clear from the

Specification or the prior art as to what relationship these tumors have to "*invasion or metastasis of the CNS*". In fact, it is compelling to the Examiner that the data presented in Table 1 (pp. 9) show evidence not of "*invasion or metastasis of the CNS*" but of a raised total CSF tau level due to the presence of tumors in the CNS. Henceforth, the Examiner has withdrawn the rejection under 35 USC §112 ¶1 of claims 1 and 5 as they pertain to CNS damage caused by tumors.

22. In addition, the patients and total tau levels presented in the instant Specification under the title "*Space Occupying Lesion, Invasion or Metastasis*" show a range of 150-335 pg/mL the sample having a median score of 292 pg/mL, a standard deviation of 75 pg/mL, and a mean (or arithmetic average) of 274 pg/mL. Thus it is not clear what statistical significance absent evidence from the prior art that can be assigned to the Applicant's assertion that 312 pg/mL is a "cutoff value" for Control patients when only 2 out of 5 patients show higher total tau levels than 312 pg/mL in the aforementioned category and both the median and mean value for the presented evidence are below the "cutoff value".

23. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that: '**b)**' patients having CNS damage with no CNS invasion show CSF-tau levels below the Applicant's assigned "cutoff value" of 312 pg/mL, (pp. 9-10 "**V. Rejection under 35 U.S.C. §112: '1. Correlation: CNS Invasion with CSF tau levels**'").

24. The Applicant's argument has been taken into consideration and is not persuasive for the following reasons. The Examiner *maintains* the rejection of claims 1, 6, and 9 under 35 USC §112 ¶1 as it pertains to "*invasions or metastasis of the CNS*". It remains unclear was to what the Applicant defines as "*invasions or metastasis of the CNS*" because the tissue origin and/or cause

of the tumors is not known. It is entirely possible that all of the CNS tumors did not result from metastasis but were in fact CNS-derived tumors. Also, the term "invasion" is not clear nor is it clear that the tumors as presented in Table 1 and Table 2 (pp. 9) where the result of or were involved in any invasion of the CNS. In fact, as the very names of the tumors imply, "medulloblastoma, germinoma, and retinoblastoma" that they are, indeed, CNS in origin. Absent evidence from the prior art or the Specification as to tissue markers or other indicators of a non-CNS origin for the tumors presented, the origin of the tumors is not self-evident. Finally, the Applicant states that "...in all cases with no CNS invasion, CSF-tau levels were low (below cutoff value)." This is not the case at hand. In the Specification, the Applicant has shown 19 patients with and without known ailments and no claimed "CNS invasion" who show CSF-tau levels that exceed the assigned "cutoff value" of 312 pg/mL, 4 of whom are listed under "Controls" (Table 4 pp. 17-19).

25. The Applicant's argument is not supported by the prior art. Nishimura et al. (April 1998) Basic and Clinical Studies on the Measurement of Tau Protein in Cerebrospinal Fluid as a Biological Marker for Alzhimer's Disease and Related Disorders: Multicenter Study in Japan." Meth. Find. Exp. Clin. Pharmacol. 20(3): 227-235 (**IDS #C2**)] teaches that patients with Alzhimer's disease have a mean tau ("total tau") level of 426 ± 234 pg/mL, patients with neurodegenerative disease have a mean tau ("total tau") level of 239 ± 157 pg/mL, patients with cerebrovascular diseases have a mean tau ("total tau") level of 216 ± 136 pg/mL, and the neurological control group has a mean tau ("total tau") level of 188 ± 103 pg/mL (Figure 5). Nishimura et al. (1998) does not put forth any evidence that the elevated levels of total tau in the Alzheimer's patients are due to "*invasions or metastasis of the CNS*".

26. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that: '**c)**' in certain patients CNS invasion would be expected, a clear correlation between CSF-tau levels and CNS damage is presented, and CSF-tau does not correspond to any particular CNS malady or injury but with the amount of CNS damage (pp. 10 "**V. Rejection under 35 U.S.C. §112: '1. Correlation: CNS Invasion with CSF tau levels'**").

27. The Applicant's argument has been taken into consideration and is not persuasive for the following reasons. The Examiner *maintains* the rejection of claims 1, 6, and 9 under 35 USC §112 ¶1 as it pertains to "*invasions or metastasis of the CNS*". Absent any evidence in the prior art or the Specification, the skilled artisan cannot rely upon "expectation" as guidance to practice the invention.

28. Concerning the correlation between elevated tau levels and CNS damage, no clear correlation was evident as discussed above.

29. The Examiner is not persuaded by the presentation that CSF-tau is indicative of a degree of amount of CSF damage. No evidence is present in the prior art or the specification as to what "degree" or "amount" of CNS damage was wreaked due to the supposed "*invasions or metastasis of the CNS*". Absent an evidence of independent markers and measures, as accepted in the art, showing that a more malignant or active "*invasions or metastasis of the CNS*" correlates to a higher CSF-tau level, a skilled artisan is presented with a daunting task of experiments to establish such a correlation to a degree of satisfaction that allows them to practice the claimed invention.

30. The Applicant traverses the 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) on the grounds that the Specification does provide working examples that show a correlation between CSF-tau levels and CNS damage caused by: (a) brain metastasis, (b) invasion or metastasis of the CNS, and (c) chemical agents (pp. 11-22 "**V. Rejection under 35 U.S.C. §112: '2. Correlation: size of infarction and CSF tau levels" 'Part 19', 'Part 20', 'Part 24', 'Parts 28 and 29', and 'In Part 32')**.

31. The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons for claims 1, 6, and 9. The Examiner *maintains* the rejection under 35 USC §112 ¶1 rejection of claims 1, 6, and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) as it pertains to CNS damage caused by brain metastasis, invasion or metastasis of the CNS, and chemical agents [listed as (a), (b), and (c) above].

32. In '**Part 19**', the Applicant traverses the rejection on the grounds that the Specification show the correlation between CNS damage cause in an individual by an invasion of the CNS and the CSF-tau level in said individual. The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons.

33. The Specification has failed to demonstrate, illustrate, or define what is meant by "*invasion of the CNS*". Furthermore no evidence is present in the prior art or the Specification as to the origin of the tumors cited as evidence or that "invasion of the CNS" in any way affects CSF-tau levels.

34. In '**Part 20**', the Applicant traverses the rejection on the grounds that the Specification demonstrates a correlation between CNS damage and CSF-tau levels for a number of tumor

metastases (Table 4). The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons.

35. Table 4 illustrates the tau levels of three patients, one with a tumor that has not metastasized, one with a tumor that has metastasized, and one with a tumor "with CNS involvement". Firstly, the last patient offers no relevant data to the argument, as there is no metastasis evident or asserted. Secondly, a single example of the control (no metastasis) and a single example of the experimental (metastasized) is not representative. Finally, the Specification passage cite by Applicant as "Example 2 (page 24, lines 3-4)" reads:

> "Two patients with rhadomyosarcoma could be analyzed at diagnosis: one patient with stage I disease had a CSF-tau level of 279 pg/mL, the other patient with stage IV disease had a level of 320 pg/mL." (pp. 24 lines 3-5)

36. Nowhere in the above quoted passage is there support to assert that the patients suffered from metastasis of a tumor or cancerous cell. Therefore, in the absence of support for metastasis affecting total tau CSF levels in the Specification as originally filed or the prior art, a skilled artisan is given no reasonable expectation of success in practicing the invention as claimed in claims 1 and 6.

37. In '**Part 24**', the Applicant traverses the rejection on the grounds that the Specification provides ample guidance to enable one of ordinary skill in the art to detect CNS damage cause by chemical agents. The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons.

38. Tables 1 and 2 illustrate various treatment regiments for patients with non-B-cell ALL/NHL and B-cell NHL. No tau levels are given to establish a nexus between the specific

pharmaceutical or chemical agent and tau levels. Therefore Tables 1 and 2 offer no data of relevance to the instant invention of claims 1 and 9.

39. The Examiner *accepts* that the Specification teaches how to measure CSF-tau levels as discussed above.

40. The cited Specification passages pp. 6 lines 6-16 and pp. 9 lines 13-17 offer prophetic guidance to practice the invention are only assertions. However, no tau levels are presented nor are any specific chemical agents outlined with their effects on CSF-tau levels. In addition, the wide breadth of chemical agents claimed by the Applicant, "*gene therapy, pharmaceuticals, chemotherapy, or exposure to chemical compounds*" cover such an immense range of conditions that it is an overwhelming burden for a skilled artisan to execute the necessary experimentation as to practice the invention within its full scope.

41. In **'Parts 28 and 29'**, the Applicant traverses the rejection on the grounds that the Applicant has overcome the rejection as discussed in **'Part 24'**. The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons.

42. The Examiner *maintains* the rejection under 35 USC §112 ¶1 rejection of claims 1 and 9 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) as it pertains to CNS damage caused by chemical agents as discussed above and therefore **'Parts 28 and 29'** are not persuasive [listed as (c) above].

43. In **'Part 32'**, the Applicant traverses the rejection on the grounds that: (a) the Specification has established a nexus or correlation between CNS damage and CSF-tau levels, (b) a skilled artisan would clearly interpret an elevated CSF-tau level in a patient known to have (or potentially have) one to the causative agents as indicting that the patient has suffered CNS-

damage induced by the causative agent, (c) the Specification clearly shows a correlation between the degree of CNS damage and CSF-tau level, (d) the Applicant clearly defines "early".

44. The Examiner *accepts* that the Specification provides guidance to measure "total tau" as asserted again by the Applicant (pp. 19).

45. As discussed above for previous grounds here reiterated by the Applicant. The Specification and prior art offer no guidance to establish a link between non-specific CNS damage, whether this question is the existence of CNS damage, the degree, or the extent. In addition, the assertions are cold comfort for the skilled artisan to practice an invention absent any definitive prior art or enabling disclosure in the Specification. Again, the Specification in Table 4 shows a broad and uncorrelated nexus between the "degree of CNS damage and CSF-tau levels". Also, the "degree of CNS damage" is not entirely clear, nor is "early".

46. The Specification fails to address contradictions in the evidence used to support claims 1, 6, and 9. For instance, what is the degree of CNS damage for the patient with bacterial meningitis with 1250 pg/mL of CSF-tau versus the patient with bacterial meningitis who has 37 pg/mL of CSF-tau? Also, what is the degree of CNS damage for the patient with myalgia, myosistis (Controls) with 435 pg/mL of CSF-tau versus the patient with myalgia, myosistis (Controls) who has 37 pg/mL of CSF-tau?

47. The Applicant continues to assert that the instant application is not intended show a correlation between any particular disorder and CSF-tau levels. This is contradictory to the prior art. For instance, Nishimura et al. (April 1998) Basic and Clinical Studies on the Measurement of Tau Protein in Cerebrospinal Fluid as a Biological Marker for Alzhimer's Disease and Related Disorders: Multicenter Study in Japan." Meth. Find. Exp. Clin. Pharmacol. 20(3): 227-235 (**IDS**

#C2)] teaches that patients with Alzhimer's disease have a mean tau ("total tau") level of 426 ± 234 pg/mL and patients with neurodegenerative disease have a mean tau ("total tau") level of 239 ± 157 pg/mL (Figure 5). It is evident from Nishimura et al. (1998) that a clear correlation between Alzhimer's disease and elevated (above "cutoff value") CSF-tau is present. It is also evident that other neurodegenerative diseases have a low CSF-tau level (below "cutoff value"). Nishimura et al. (1998) includes Pick's disease, Lewy body disease, frontal-lobe dementia, and corticobasal degeneration as "neurodegenerative diseases", each of which by definition causes CNS damage (pp. 229). Therefore, the Applicant's assertion that high-CSF tau is indicative of general CNS damage and not specific forms of CNS damage contradicts the prior art.

48. In regards to "early", the Applicant cites the Specification (pp. 7 lines 10-13:

> "'[e]arly detection and/or quantification of CNS damage' means that the CNS damage is determined by a method that allows it to be detected before it is detectable by current methods."

49. The above statement has not clear meaning because no specific method or detection parameters are presented. The Applicant in claims 1, 6, and 9 has ascribed the measurement of CSF-tau as a method of diagnosis for a wide range of diseases, disorders, and ailments. The clinical definition of "early" varies on a case-to-case basis and thus the skilled artisan is confronted with the undue burden of determining what is considered "early" for each condition through trial and error. Further, no clear examples of what is "early" are given.

50. The Applicant continues to assert that the Specification shows:

> "**a)** The detection of high CSF-tau levels in patients with CNS damage (where the CNS damage is also detectable by other methods available at the time the application was filed).
> **b)** The detection of low-CSF-tau levels in patients where no CNS damage is either known or expected to exist (and which is not detectable by other available methods).

> **c)** The detection of high CSF-tau levels in patients where CNS invasion could be expected to occur (*e.g.* in a disease where CNS damage is expected as the disease progresses), but which is not yet detectable by classical means. Applicant notes that it would have been possible to detect the CNS damage by classical methods if the disease had been allowed to progress (to confirm Applicant's observations). However, it would have been both unethical and clinically imprudent to allow invasion to progress to such a more advanced state. Therefore, once an elevated CSF-tau level was detected, the patients were treated to prevent further invasion, and thereby, prevent additional CNS damage." (pp. 20)

51. The Examiner *accepts* that both CSF-tau levels can be measured and that medical professionals could assess CNS damage at the time of the invention as asserted in "**a)**".

52. The Examiner is unable to determine of what value CFG-tau levels are purported to be of in this statement since "high CSF-tau" levels or those above the "cutoff value" of 312 pg/mL were reported in four "Control" patients. Most notably, Table 4 (pp. 19) shows a patient with "carpal tunnel syndrome" as having a high CSF-tau level of 665 pg/mL in relation to "**b)**".

53. The Examiner is unable to determine from the Specification to which "disease" the Applicant refers to in "**c)**" therefore no value can be assigned to this statement.

54. Finally, The Applicant also reviews the art cited by the Examiner as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) and either affirms or dismisses each in turn (pp. 19-22). The Applicant's argument has been taken into consideration and is not *persuasive* for the following reasons.

55. The Examiner accepts the Applicant's interpretation of the following references:

a. Arvanitakis and Wszolek (2001)

b. Spilantini and Goedert (1998)

c. Galasko (2001)

d. Pilkington et al. (1997)

e. Dengler et al. (1998)

f. Zhang and Toumanen (1999)

56. The Examiner does not accept the Applicant's interpretation of the following references:

57. Kapaki et al. (2000) reports that CSF-tau levels are may be indicative of axonal impairment in multiple sclerosis patients. Yet Kapaki et al. (2001) reports that multiple sclerosis patients showed 249.6 pg/mL, well below the Applicant's "cutoff value" of 312 pg/mL therefore offers contradictory evidence (Abstract). Also, Jiménez-Jiménez et al. [(2002) "Tau protein concentrations in cerebrospinal fluid of patients with multiple sclerosis." Acta. Neurol. Scand. 106(6): 351-4] report that CSF tau concentrations are not a maker of multiple sclerosis. Jiménez-Jiménez et al. (2002) reports MS patients showing 233.7 pg/mL, well below the Applicant's asserted "cutoff value" of 312 pg/mL (Table 1). Therefore, the art is contradictory.

58. Molina et al. (1997) the Applicant dismisses the fact that Molina et al. (1997) reported that patients Parkinson's disease (PD) without dementia do not show elevated CSF-tau levels. Contrary to the Applicant's statement, "CNS damage" is implicit to the definition of PD as it is caused by the degeneration of dopaminergic neurons [Kandel et al. "Principles of Neural Science." (pp. 50 and 862-865)]. It is important to note that Molina et al. (1997) discusses how CSF-tau levels are not correlated to the onset of PD, the duration of PD thus refuting the Applicant's assertion that CSF-tau levels can be correlated to the degree or extent of CNS damage in a general sense. Further Molina et al. (1997) also notes that no relation between antiparkinsonian drugs and increased CSF-tau levels therefore refuting the Applicant's claimed invention that CSF-level are associated with chemical agents (Abstract). Therefore this reference

supports the Examiner's argument that elevated CSF-tau levels are not indicative of CNS damage in general but are indicative of specific conditions.

59. Ellis et al. (1998) reports that subjects with HIV-associated neurocognitive disorders where similar to those that are HIV-negative as are HIV-positive subjects with peripheral neuropathies versus those without neuropathies. It is of note that HIV-positive with peripheral neuropathies showed an above cutoff value of 320 pg/mL but Ellis et al. (1998) did not hold this to be significant over the control group (Abstract). Therefore this reference supports the Examiner's argument that elevated CSF-tau levels are not indicative of CNS damage in general but are indicative of specific conditions.

60. Bitsch et al. (2002) discusses the correlation between elevated tau levels and ischemic stroke. Bitsch et al. (2002) is a post-filing enabling reference for claims 1 and 8 concerning ischemia stroke. The Examiner has already withdrawn the rejection under 35 USC §112 ¶1 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) of claims 1 and 8 therefore the argument is *moot*.

61. Süssmuth et al. (2001) does not provide evidence to support the Applicant's assertion that increased CSF-tau is a marker of general CNS damage and can be correlated to the extent or degree of CNS damage. Finally, Süssmuth et al. (2001) actually teaches that CSF-tau is elevated in some not all instances of CNS damage. Süssmuth et al. (2001) is a post-filing enabling reference for claims 1 and 8 concerning cerebral hemorrhage. The Examiner has already withdrawn the rejection under 35 USC §112 ¶1 as set forth in at pp. 4-18 ¶9-32 of the previous Office Action (Paper No. 8, 12 March 2003) of claims 1 and 8 therefore the argument is *moot*.

62. Therefore, the rejection of claims 1, 6, and 9 under 35 USC 112 ¶1 is maintained.

New Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

63. Claims 1, 8, and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5861257 in view of Strand et al. (1984) "Brain and Plasma Proteins in Spinal Fluid as Markers for Brain Damage and Severity of Stroke." Stroke 15(1): 138-144.

64. US 5861257 teaches the use of a monoclonal antibody produced by the hybridoma AT120 to detect tau protein in samples of cerebrospinal fluid to detect a disease in a patient suspected of suffering from Alzheimer's disease or any other disease involving alterations in tau protein (claim 1).

65. Regarding "*any other disease involving alterations in tau protein*", Strand et al. (1984) teaches that tau protein is increased in the cerebrospinal fluid of patients suffering from stroke related CNS damage including cerebral infarction and cerebral hemorrhage thus meeting the limitations of claims 1 and 8 (Table 1).

66. While the claims are not identical, the method steps are similar and the scope of diseases sought to be detected via tau immunocytochemistry are similar.

67. Claims 1, 5, and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5861257 in view of Shoji et al. (30 June 1998) "Combination Assay of CSF Tau, Aβ1-40, and Aβ1-42(43) as a biochemical marker of Alzheimer's disease." Journal of Neurological Sciences 158: 124-140.

68. US 5861257 teaches the use of a monoclonal antibody produced by the hybridoma AT120 to detect tau protein in samples of cerebrospinal fluid to detect a disease in a patient suspected of suffering from Alzheimer's disease or any other disease involving alterations in tau protein (claim 1).

69. Regarding "*any other disease involving alterations in tau protein*", Shoji et al. (1998) teaches that tau protein is increased in non-AD related neurological diseases (pp. 136). In Table 1 Shoji et al. (1998) includes a patient with a brain tumor in the "other neurological disease group" thus meeting the limitations of claims 1 and 6 (Table 1).

70. While the claims are not identical, the method steps are similar and the scope of diseases sought to be detected via tau immunocytochemistry are similar.

Summary

71. Claims 1, 5, 6, 8, 9, and 11 are rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
March 28th, 2003